

When Should Children with HIV Infection Be Started on Antiretroviral Therapy?

Steven B. Welch, Di Gibb

Background to the debate: The advent of highly active antiretroviral therapy (HAART) dramatically improved the prognosis for both adults and children infected with HIV who had access to treatment. However, the optimal timing for initiating treatment remains controversial, particularly in children. This debate lays out the case for deferred treatment against the case for early initiation of HAART in children.

Steven Welch's Viewpoint: The Case for Deferring Treatment

Combination antiretroviral therapy (ART) has transformed paediatric HIV infection in developed countries in the last decade, and has the potential to do so worldwide. Paediatric HIV has gone from being universally fatal to becoming a treatable chronic condition. A child diagnosed with HIV in a developed country in 2007 would be expected to survive into adulthood, largely thanks to ART. With the privilege of being able to prescribe such successful treatment comes the responsibility of using it wisely. When they leave our care for adult clinics, our paediatric patients should have been optimally treated and have a good understanding of their condition. The hasty and injudicious use of ART risks creating a cohort that has learned poor adherence habits, is infected with multi-drug-resistant viruses, and has been exposed to unnecessary cumulative drug toxicities.

Infants are unique because of their high susceptibility to life-threatening opportunistic infections or irreversible brain damage from HIV encephalopathy during a critical developmental period. Their CD4 counts and percentages are also less dependable predictors of complications at this age. There is thus an increasing consensus and supporting evidence in favour of early, perhaps universal treatment of children aged less than one year [1]. However, we treat infants in the confessed knowledge that 80% of them do not have rapidly progressive disease, accepting that we are not good enough at recognising complications such as encephalopathy before irreversible damage has been done. Beyond infancy, we should delay treatment until it is really needed—for children older than a year, rapid progression without easily detectable clinical changes or a fall in CD4 count is less likely.

Ideally, we would base our decision on when to start treatment on data from randomised controlled trials, but these do not exist. In their absence, it is tempting to get all children established on treatment. Are there any reasons not to do this? On the principle of "*Primum non nocere*" (First,

do no harm), we should not treat children unless there is evidence they will benefit. But what harm can ART do?

Children diagnosed with HIV may now live for many decades. There are no data on the cumulative effects of taking ART for decades, because these drug combinations have only been available for just over one decade. But it is clear that some side effects, particularly dyslipidaemias and the accumulation of cardiovascular risk, do depend on duration of drug exposure. Anything we can do to lessen this duration must be beneficial. Structured treatment interruptions for adult patients went out of favour following the results of the recent Strategies for Management of Antiretroviral Therapy (SMART) study [2]. In the SMART study, structured treatment interruptions significantly increased the risk of opportunistic diseases or death from any cause, as compared with continuous ART. We await the outcome of the PENTA 11 study (Paediatric European Network for Treatment of AIDS) of treatment interruptions in children (see <http://www.pentatrials.org/trials.htm#penta11>), but for now we must assume that once a child has been started on treatment it is likely to be lifelong. The only way of minimising drug exposure is therefore to avoid starting treatment too early.

The effect of taking ART on family life cannot be overstated. Sadly, HIV remains a stigmatised condition, and many families choose not to disclose their diagnosis to even close contacts. The mere presence of medication in the house risks accidental discovery and inadvertent disclosure. Most schools are not aware of children's diagnoses, and sending children to sleepovers or on school trips may become a major problem. Many families report missing doses when they cannot be taken unobserved rather than risking discovery. Unlike other chronic conditions, successful treatment of HIV requires drug adherence rates of the order of 95%

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Abbreviations: ART, antiretroviral therapy; CHER, Children with HIV Early Antiretroviral Therapy; HAART, highly active antiretroviral therapy; PENTA, Paediatric European Network for Treatment of AIDS; SMART, Strategies for Management of Antiretroviral Therapy

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[3]. Failure to achieve this risks rapid evolution of drug-resistant virus. Palatable paediatric syrups and appropriate low-dose tablet formulations remain all too rare, meaning that adherence is more difficult for children than adults. Add in the difficult social situations of many families living with HIV, and the fact that some paediatric antiretroviral syrups still need refrigeration, and it is clear that maintaining drug adherence can be a massive undertaking. Imposing this burden if it is not truly necessary creates a risk of learned poor drug adherence practices, and the limitation of future treatment options because of drug resistance.

Worldwide, the greatest obstacle to ready availability of ART for children is cost, and where drugs are readily available we have the responsibility to use them wisely. This includes not wasting this expensive resource when it is not really indicated. ART should never be initiated lightly in children, and, beyond infancy, should only be started when the individual child's clinical condition and CD4 count indicate a clear likelihood of the benefit outweighing the possible harm.

At which CD4 count this benefit occurs is not clear. We rely on cohort data from before the era of HAART to inform us of the risk of short-term disease progression for a child of a given age with a particular CD4 count [4,5]. But we have no data on the long-term outcomes of starting ART at different CD4 counts. It therefore remains rational to consider an individual child's and family's wishes and circumstances as well as the child's risk of disease progression in deciding when to start treatment, rather than using a rigidly set CD4 threshold.

Di Gibb's Viewpoint: The Case for Earlier Initiation

The debate about when to start ART has raged since effective triple combination ART became available over a decade ago. At that time, the hope of HIV eradication fuelled enthusiasm for liberal use of ART [6]. However, with the rapid realisation that HIV could not be cured, and fears about toxicity of early drugs and HIV resistance, in the late 1990s, there was a swing to the other extreme—starting ART “as late as possible” [7].

In the last eight years, arguments for delaying ART have become weaker and those favouring earlier ART have strengthened for both adults and children. New evidence shows that progression to AIDS and, in particular, serious non-AIDS events (cardiac, renal, hepatic) occur at higher CD4 thresholds than previously thought [2]. This is particularly true for middle-income countries and resource-limited settings, where most HIV-infected children live [8]. Moreover, early fears about long-term drug toxicity were probably overplayed [9]; more appropriate, simpler drug regimens have become increasingly available, resulting in year-on-year improvements in durable viral load responses [10]. Finally, triple-class drug resistance appears less common than originally anticipated [11], and two new classes of drugs, with no cross-resistance, have recently become available.

The goals of ART are to save lives, decrease morbidity, minimise toxicity, and maximise quality of life. For HIV-infected children, there is also the need to achieve full future potential as adults, in terms of growth, pubertal development, and neurodevelopment. I would argue that

earlier ART for children is even more important than for adults for five reasons. First, HIV disease progression is faster in young children than in adults [12]. Second, significant immune recovery is better in younger children in whom the thymus is more active [10,13]. Third, bacterial infections are most common and serious in younger children, occur at high CD4 values, and are reduced by ART [14]; the same is true for tuberculosis, of particular relevance to resource-limited settings [15]. Fourth, better growth occurs if ART is started early; untreated children are ten centimetres shorter than their uninfected peers by age ten years [16], and short stature may be harder to reverse when ART is started at older ages. Fifth, HIV encephalopathy is a particular concern for children exposed to HIV during brain development; early ART initiation appears to reduce HIV encephalopathy compared to historical controls in infants [1,17], and may also reduce more subtle neurological problems in older children.

In addition to these arguments, many of which are based on data from cohort studies, which can be prone to several forms of bias, new randomised evidence has recently been presented that reinforces the arguments for earlier ART. Initial data from the Children with HIV Early Antiretroviral Therapy (CHER) trial recently showed a highly significant 76% reduction in mortality in infants initiating ART before 12 weeks of age, compared with starting when CD4 percentages fell below 25% or clinical symptoms developed [1]. Of note, deaths were sudden and often not strictly AIDS-defining. CHER is continuing, with the objective of evaluating the long-term effects of early limited ART; young infants in the deferred arm have been started on ART.

What about children after infancy? Risk of disease progression decreases with age in childhood [18,19], so first let us consider children over five years. Evidence from a recent study combining data on untreated children over five years from the HIV Paediatric Prognostic Markers Collaborative Study [18,19] and data from adults (Concerted Action on SeroConversion to AIDS and Death in Europe, CASCADE) shows that the risk of disease progression according to current CD4 cell count (rather than CD4 percentage, as used in younger children) is almost identical in a five-year-old and in a young adult [20]. Thus, any arguments suggesting that ART should be initiated earlier in adults are of equal relevance to older children.

New randomised evidence has recently been presented from a subgroup of about 500 adults who were ART naïve or had not received ART for over six months at enrolment in the SMART trial [21]. Patients with CD4 counts over 350 cells/mm³ randomised to delay ART had a significant (approximately 5-fold) increased risk of both AIDS and serious non-AIDS events compared with those starting ART at CD4 counts over 350 cells/mm³. In effect, this was a mini “when to start” randomised trial. These data are further supported by recent cohort analyses showing a continuum of decreasing disease progression among patients not on ART at CD4 cell counts below 350 compared with those with CD4 counts between 350–500, in turn compared with those with CD4 counts above 500 [22]. This suggests the need for revision of adult and older children guidelines to advocate ART initiation by the time a patient's CD4 count has reached 350 cells/mm³, rather than when it is between 200–250 cells/mm³, as previously recommended [23,24]. Randomised

trials are also needed, and could include older children, but should focus on evaluating starting ART at even higher CD4 counts [25].

Finally, I appreciate that the prospect of “therapy for life” is daunting for caregivers and paediatricians. Nevertheless, it is important to remember that short stature, delayed puberty, and difficulties with school—both academic and social—can only add to the miseries of living with HIV during adolescence, which is anyway a time when adherence to drugs becomes worse. Therefore, rather than deferring ART for as long as possible, I would argue that a better strategy might be to maximise the potential of ART to fully suppress viral load and to normalise the immune system, growth, and neurodevelopment during early childhood when carers can more easily supervise ART, followed by simplifying or even interrupting regimens during adolescence (if ongoing trials such as PENTA 11 show this is safe). We need trials to evaluate starting ART at even higher CD4 counts (in older children) and higher CD4 percentages in younger children, and more work is needed to compare the predictive value of CD4 count and percentage in young children. In the meantime, deferring treatment initiation for as long as possible is no longer an option, and paediatric guidelines need to be updated now. Indeed, European adult guidelines now recommend ART initiation at CD4 counts below 350 cells/mm³ [26].

Steven Welch’s Response to Di Gibb’s Viewpoint

The most convincing data in favour of early treatment come from adults and infants, and there are good reasons why these may not apply to older children. Professor Gibb’s other arguments for early initiation of ART in children are based on the perceived safety of new drug regimens, the need to maximise children’s growth and developmental potential, and the risk of clinical progression.

Adults starting ART have poorer immune reconstitution if they start at low CD4 counts, but in children, long-term immune reconstitution is independent of CD4 count [27,28] or age [28] at start of treatment. Starting treatment at young age does increase the risk of poor virological response, and hence resistance [13]. Professor Gibb argues that data from the SMART study [21] on treatment thresholds in adults can be applied to children, based on pre-HAART comparisons of CD4-related short-term AIDS progression risks in adults and children [20]. But similar progression risks do not equate to similar benefits from treatment. Much of the benefit from treatment in the SMART study was from avoidance of non-AIDS events. These include cardiovascular events and malignancies, which occur much less commonly in children than in adults.

The recent advent of new drugs and drug classes to treat HIV is very welcome, but we must be wary of excessive therapeutic optimism. The advent of HAART was followed by a trend for its early use, followed by a swing to the other extreme. Children starting ART will be taking drugs for decades, and we cannot be certain about long-term safety after a couple of years.

The risks of rapid disease progression, including encephalopathy, are alone enough to warrant aggressive early treatment of HIV in infants. The data from the CHER

trial [1] further reinforce this argument, but make no contribution to the debate in older children. Many factors contribute to poor nutritional, growth, and developmental outcomes in children with HIV, and a far broader approach than the provision of ART will be required to optimise these outcomes.

The fact that guidelines have fluctuated so much over time between recommending early and late treatment demonstrates that we still do not know the right time to start. There are good reasons not to extrapolate adult and infant data to older children. What is needed is a proper randomised trial of thresholds for initiating treatment in children [29]. Until the results of such a trial are available, it remains appropriate to decide the right time on an individual basis for each child and their family, taking into account the family’s wishes and circumstances as well as the child’s CD4 count.

Di Gibb’s Response to Steven Welch’s Viewpoint

Dr. Welch agrees that there is good evidence for starting early ART in infants [1]. Data in adults are also compelling, as evidenced from recent presentations at the 2008 Conference on Retroviruses and Opportunistic Infections (<http://www.retroconference.org/2008/>) showing that non-AIDS serious events at high CD4 cell counts may well be HIV-related rather than drug-related [30]. For well-resourced settings, adult guidelines have recently changed to recommend treatment initiation in individuals with CD4 counts of less than 350 cells/mm³ (previously those with CD4 cell counts of between 200–350 cells/mm³ were “for consideration of ART” rather than “recommended”). As I have argued, children over five years in well-resourced settings have similar risks of disease progression as young adults at the same CD4 count [20]. It is untenable for older children to initiate ART later than adults. Indeed, new US data suggest that, as in adults, CD4 recovery in children may be related to the baseline CD4 count before initiating HAART: recovery is poorer if the CD4 percentage is under 15% [31]. The risk of disease progression is higher in one-to-five-year-olds than older children; it follows that the CD4 thresholds for ART initiation in one-to-five-year-olds should be higher to reflect this greater risk.

Poor availability of ARV drug formulations is not a reason to defer ART. Rather, arguments for the need for therapy should spur paediatricians and children’s activists to lobby pharmaceutical companies to make more appropriate drug formulations and ensure timely availability of paediatric pharmacokinetic data. New European law and World Health Organization recommendations on use of simplified dosing tables based on weight-bands, derived from body surface area, should help in this regard [32]. Both originator and generic pharmaceutical companies are beginning to respond to such lobbying.

There remains an urgent need for large randomised trials on timing of ART initiation in both well-resourced and resource-limited countries. In well-resourced settings, I would argue that evaluating ART initiation at high CD4 counts versus below the 350 cells/mm³ CD4 count threshold in older children and adults would be appropriate. A separate trial with higher control thresholds (as CD4 percentage) is needed for children aged one to five years. Neurodevelopmental

and growth evaluations would be key endpoints for children. For resource-limited settings, issues include the role of ART in reducing HIV transmission, prevention of tuberculosis, and malnutrition [8]. Separate trials on the “when to start” question in resource-limited settings need to address these issues. In addition, when choosing thresholds here, consideration must also be given to ART availability and cost-effectiveness, as currently fewer than 20% of sick adults and even fewer children in urgent need of ART receive such treatment.

Paediatric guidelines for infants in the first year of life should now recommend universal ART where infant diagnosis is available; implementation and cost-effectiveness need examining in settings where early diagnosis is not available. Finally, the question about whether ART can be stopped after having been started soon after seroconversion in all infants needs to be addressed.

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